JOURNAL OF CLINICAL RESEARCH BEST PRACTICES

Vol. 10, No. 9, September 2014 "Happy Trials to You"

What's New in GCP?
FDA Updates Informed Consent Guidance

Reprinted from the Guide to Good Clinical Practice with permission of Thompson Publishing Group, 805 15th St., Washington, D.C. 20005; www.thompson.com. To learn more about the Guide to Good Clinical Practice, visit: www.firstclinical.com/gcpguide.

The FDA released draft guidance on informed consent on July 15.

The FDA said the existing guidance, which was issued in 1998, needed to be "substantially revised due to changes in regulation/regulatory policy and in response to numerous questions about informed consent from subjects, subject advocates, and the research community."

"This is something that the FDA targeted about a decade ago," Joanne Less, the director of FDA's Good Clinical Practice program, said July 21. "We were trying to give advice, partly for our own staff about what we were expecting our staff to look at and also to let the IRB and sponsor communities know" the agency's thinking.

Less said after the FDA started revising the guidance, several groups asked the agency to provide guidance on specific issues, such as termination of research and wards of the state.

"We tried to put it together in one document so it would all be in one place, but then that takes time to get cleared," Less said.

The new guidance includes a more detailed discussion of informed consent for non-English-speaking subjects, impaired consent capacity, and subjects with low literacy or numeracy. The draft guidance also addresses the new element of consent that indicates information on the trial will be posted on ClinicalTrials.gov and discusses informed consent issues related to children as subjects, review of patient records, subjects participating in more than one clinical trial, and study suspension/termination. The draft guidance also explains the responsibilities of the IRB, investigator, sponsor and FDA related to the development and review of informed consent documents.

A notice (79 Fed. Reg. 41291) said the guidance will assist institutional review boards, clinical investigators, and sponsors in carrying out their informed consent responsibilities under 21 C.F.R. Part 50 by providing recommendations on the informed consent process, elements of informed consent, and the documentation of informed consent to assure the protection of the rights and welfare of human subjects in clinical investigations.

The FDA noted that it is working with the HHS Office for Human Research Protections (OHRP) to ensure harmonization of the agencies' regulatory requirements and guidance and that HHS is working on revising the Common Rule. "FDA issued this draft guidance while the agencies continue to explore potential changes to the Common Rule. To the extent that issues presented in this draft guidance intersect with the Common Rule, FDA plans to coordinate with other relevant federal agencies to facilitate consistency across policies," the notice said.

When finalized, the guidance will supersede the FDA Information Sheet, "A Guide to Informed Consent," and the sections on the informed consent process in its "Frequently Asked Questions."

Subject Participation in Several Trials

Although the FDA said that it "strongly discourages subjects from participating simultaneously in more than one clinical trial or enrolling in a single clinical investigation multiple times," the agency does not provide much guidance on how to combat such practices.

"Investigators should inquire about multiple enrollments and discourage this practice in the consent form and during any informed consent discussions," the draft guidance said. It added that sponsors generally include prohibitions related to the use of concomitant medications in the protocol or restrict inclusion of subjects who have participated in another clinical investigation within a specified period of time. "Implied in the prohibitions on concomitant medications is the idea that subjects should not participate in more than one clinical investigation at a time," the guidance said.

What To Say about Suspension or Termination of a Study

When studies are suspended, IRBs, sponsors and investigators should consider whether subjects should be notified, and if so, when, given that complete information may not be available. "All parties should consider what information should be shared with subjects to ensure that their rights and welfare are protected, that they are not put at risk, and that they receive appropriate care, if indicated."

The parties involved, including the subjects' treating physicians if different from the investigator, as appropriate, may need to determine whether it is in the best interests of the enrolled subject to continue receiving the interventions at the present site, be transferred to another study site so that participation may continue, or be transitioned to medical management outside of the research.

"Continuation of subjects on the test article may be appropriate, for example, when the test article holds out the prospect of direct benefit to the study subjects or when withholding the test article poses increased risk to study subjects. In general, information about these considerations should be shared with subjects so that they may understand the changes affecting their participation in the study and allow them to make informed decisions about their continued participation."

If a study is terminated, study subjects should be provided with as much information as possible regarding the reason for the termination, the guidance said. "Such a discussion not only recognizes their valuable participation in the study but also helps explain the scientific value of the information obtained due to their willingness to participate in clinical research. Moreover, such a discussion provides an opportunity to address questions subjects may have about the investigational product that was administered to them (e.g., immediate safety concerns, ability to participate in another clinical trial, and appropriate waiting period to do so) and what long-term follow up may be available or necessary."

The guidance added that if the study is terminated for a safety concern that may affect the future medical care of the subject, "appropriate follow-up procedures would need to be discussed with the subjects and possibly the subject's primary care provider."

Data Retention After a Subject Withdraws

Under FDA regulations, data collected on subjects up to the time of withdrawal from a clinical investigation must remain in the study database (21 C.F.R. §312.62(b) and 21 C.F.R. §812.140(a)(3)). "Subjects should be advised in the consent document that the data collected on them up until the point of their withdrawal remains part of the study database and may not be removed. An investigator should ask a subject who is withdrawing whether

he/she wishes to withdraw from the investigational interventions only and is willing to continue in the clinical investigation for follow up of associated clinical outcome information," the guidance said.

If a subject withdraws from the interventional portion of the clinical investigation but agrees to continued follow up not addressed in the original consent form, "the investigator must obtain the subject's informed consent for this limited participation using an IRB-approved consent form (21 C.F.R. §50.25(a)(1))."

If a subject withdraws from the interventional portion of a trial and does not consent to continued follow up of associated clinical outcome information, "the investigator must not access the subject's medical record or other confidential records that would require additional consent from the subject (21 C.F.R. §50.20 and 21 C.F.R. §50.25(a)(1). However, such records may be accessed consistent with the original consent process, without additional consent, to obtain information collected prior to the subject's withdrawal from the study," the guidance said.

An investigator may consult publicly available sources of information to determine a subject's vital status (and if deceased, cause of death) after a subject withdraws from a clinical investigation, and this does not require subject consent because the information is publicly available.

Review of Patient Records

Whether the record review is considered part of the clinical investigation under 21 C.F.R. §50.3(c) and 21 C.F.R. §56.102(c) is determined on a case-by-case basis. If the record review is part of the clinical investigation, then informed consent from the subject for the record review is required under 21 C.F.R. Part 50.

A survey of patient records at a site may be conducted to determine whether a site has a sufficient number of patients for the study. "Such a survey is in preparation for a clinical investigation and does not fall within the definition of a clinical investigation and, therefore, does not require informed consent under FDA's regulations," the guidance said. However, investigators and sponsors must comply with all applicable HIPAA privacy protections.

A patient's records also may be reviewed to determine whether the patient is eligible for a study, and limited information about the potential subject may be recorded. "It should be noted, however, that only information to establish the patient's eligibility for the study and contact information should be recorded," the guidance said.

"This preliminary review of the patient's record and recording of limited information is considered preparation for a clinical investigation, does not fall within the definition of a clinical investigation, and does not require informed consent. Even though informed consent is not required by FDA in these instances, proper maintenance of these records includes safeguarding the privacy and confidentiality of the patient's information," the guidance said.

If a patient's record does not include the basic information needed to determine if he or she is eligible for the study, additional information may need to be gathered from the potential subject and may require obtaining informed consent. FDA said more information can be found in its information sheet on screening tests prior to study enrollment.

The guidance said the records of a subject previously enrolled in a study may be reviewed retrospectively, without re-consenting the subject, to collect additional information under limited circumstances that are consistent with the original consent. "If this retrospective review is to gather information that was intended to be collected but was missed, then this review is considered to be covered by the previous informed consent" and additional consent is not required.

However, if the additional information goes beyond what was identified in the original protocol and disclosed in the original consent form, obtaining informed consent would be required (21 C.F.R. §50.20 and 21 C.F.R. §50.25). "Where possible, FDA recommends that the clinical investigator anticipate the need for obtaining further information and obtain consent as part of the initial consent process."

Clinical investigators, sponsors and institutions also need to consider whether institutional policies or other statutory or regulatory requirements exist, such as HIPAA and the Common Rule.

Reporting Aggregate Results

The FDA noted that subjects are frequently interested in the aggregate results of their research. "Aggregate research results should be returned to subjects in a clear and comprehensible manner. Some trials are required to register and submit summary results to ClinicalTrials.gov and FDA requires a specific statement in the informed consent about this.

For trials that are not required to register and submit results to ClinicalTrials.gov, the guidance said the trial sponsor or principal investigator may voluntarily register and report results to the databank. "If a sponsor or principal investigator plans to submit trial results voluntarily, nothing would prevent an investigator, sponsor or IRB from informing potential subjects of the plan to submit such information in an appropriate manner. Informed consent forms can direct subjects to www.ClinicalTrials.gov, where subjects can obtain certain overall study results. Investigators and sponsors can describe other plans in the consent document for informing subjects of the outcomes of the clinical investigation," the guidance said.

Submit electronic comments to www.regulations.gov citing FDA-2006-D-0031 by Sept. 15.

To Find Out More

The notice is available at http://www.gpo.gov/fdsys/pkg/FR-2014-07-15/pdf/2014-16492.pdf.

The guidance is available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM405006.pdf.

Other Recent Developments in the Guide to Good Clinical Practice

FDA Bioresearch Monitoring Inspections Remain Constant in FY 2013

SACHRP Examines Return of Research Results

EMA Board Delays Formal Adoption of Clinical Trial Data Policy to October